Office Action Summary	Application No.	Applicant(s)	
	09/512,568	HEIN ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,24-40,43,50,54-63,69-80,101 and 102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,24-40,43,50,54-63,69-80,101 and 102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed May 6, 2003, paper no. 27, has been entered.

Claims 1-20, 22-23, 41-42, 45-49, 51-53, 64-68 and 81-100 are cancelled.

Claims 21, 69 and 80 are newly amended.

Claims 101 and 102 are newly added.

Claims 21, 24-40, 43, 50, 54-63, 69-80 and 101-102 are pending and are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 24-27, 29-30, 39-40, 78, 80 and 101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to plant cells containing nucleotide sequences encoding a biologically functional multimeric protein comprising at least two different polypeptides not normally produced by plants, and the biologically functional multimeric protein encoded by said

sequences, including a multimeric protein comprising a ligand binding polypeptide, a multimeric protein comprising an antigen binding polypeptide, a multimeric protein that forms a binding site for a predeterimined antigen, a multimeric protein that is an enzyme, a multimeric protein that contains one or more disulfide bonds, and a multimeric protein wherein the polypeptides are joined by hydrogen bonding.

In contrast, the only plant cells described and characterized in the specification are plant cells containing nucleotide sequences encoding catalytic and secretory antibodies (pages 52-102). While the specification indicates that plant cells containing nucleotide sequences encoding other multimeric proteins such as enzymes and ligand binding receptors could also be prepared (page 15 lines 8-14; page 16 lines 4-10; page 29 line 30 through page 30 line 9; page 46 lines 24-25), the specification does not describe or characterize plant cells containing nucleotide sequences encoding any type of multimeric protein other than antibody proteins. This description does not constitute a substantial portion of the genus that comprises nucleotide sequences encoding all non-plant multimeric proteins comprising at least two different polypeptides, or the genus that comprises nucleotide sequences encoding all non-plant multimeric proteins comprising a ligand binding polypeptide, or the genus that comprises nucleotide sequences encoding all non-plant multimeric proteins comprising an antigen binding polypeptide, or the genus that comprises nucleotide sequences encoding all non-plant multimeric proteins that form a binding site for a predeterimined antigen, or the genus that comprises nucleotide sequences encoding all non-plant multimeric enzyme proteins. Each of the claimed genera encompass a vast array of structurally and functionally different nucleotide sequences and proteins, including those yet to be discovered. The disclosure of plant cells containing nucleotide sequences

encoding a single type of non-plant multimeric protein (antibodies) does not provide an adequate description of the claimed genera, and in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of plant cells containing nucleotide sequences encoding all non-plant multimeric proteins comprising at least two different polypeptides (see Written Description Guidelines, Federal Register, Vol. 66, No. 4, January 5, 2001, pages 1099-1111).

Claims 21, 24-40, 43, 50, 54-63, 69-80 and 101-102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the exemplified plant cells containing antigen-specific antibodies, does not reasonably provide enablement for plant cells containing nucleotide sequences encoding any non-plant biologically functional multimeric protein, assembly of any two polypeptides to form a multimeric protein, or for transgenic plants in which any non-plant biologically functional multimeric protein is present at a level of at least 56 ng/mg of total protein in its extract. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to plant cells containing nucleotide sequences encoding a biologically functional multimeric protein comprising at least two different polypeptides not normally produced by plants, and the biologically functional multimeric protein encoded by said sequences, including a multimeric protein comprising a ligand binding polypeptide, a multimeric protein comprising an antigen binding polypeptide, a multimeric protein that forms a binding site for a predeterimined antigen, a multimeric protein that is an enzyme, a multimeric protein that

contains one or more disulfide bonds, and a multimeric protein wherein the polypeptides are joined by hydrogen bonding. The claims are also drawn to plant containing nucleotide sequences encoding an antigen-specific immunoglobulin. The claims are additionally drawn to transgenic plants in which multimeric protein or antigen-specific immunoglobulin is present at a level of at least 56 ng/mg of total protein in a plant extract.

While the specification discloses the expression of catalytic and secretory antibodies in transgenic tobacco plants (pages 52-102), and the level of expression of secretory IgA and individual immunoglobulin light and heavy chains in transgenic tobacco plants (page 68 Table 3; page 69 Table 4; page 89; page 99), the specification does not disclose the expression of any other type of non-plant multimeric protein in plant cells.

While one of skill in the art could readily make transgenic plants plant cells containing nucleotide sequences known to encode the different polypeptides present in any non-plant multimeric protein, it would require undue experimentation for one skilled in the art to determine how to express those polypeptides in a manner that would allow for the proper assembly of the non-plant multimeric protein in a plant cell, because expressing the different polypeptides in a manner that would allow for their assembly in a plant cell is unpredictable, as numerous variables may affect assembly, including but not limited to the level and location of expression as well as the presence of other cellular factors that may be required for multimer assembly.

Proper assembly of a non-plant multimeric protein in a plant cell may require the expression of each different polypeptide at a particular level that is unique to the particular polypeptide and its corresponding multimeric protein, as some multimeric protein subunits are known to accumulate at different levels under native conditions. For example, Lippincott-

Schwartz et al. teach that five T cell receptor subunits (α,β,γ,δ,ε) are synthesized in excess (70-90%) over the ζ T cell receptor subunit, and that a subpopulation of pentamers assemble with the limiting ζ chain to form the complete heptameric T cell receptor complex (α,β,γ,δ,ε, ζ_2) (Cell, 1988, Vol. 54, pages 209-220, see page 209 column 2 first paragraph).

Proper assembly may also require the expression and/or presence of each different polypeptide in the same cell or cellular compartment, as the stability of the different polypeptides or their proper assembly may require their coexpression. For example, Waldeman et al. teach that while coexpression of a sodium channel γ subunit with a sodium channel α subunit increases currents in oocytes over currents induced by expression of the α subunit alone, coexpression of both a sodium channel β subunit and γ subunit with a sodium channel δ subunit (homologous to the sodium channel α subunit) was required to increase currents in oocytes over currents induced by expression of the δ subunit alone (The Journal of Biological Chemistry, 1995, Vol. 270, No. 46, pages 27411-27414, see page 27413 column 1 second paragraph). As another example, Bonifacino et al. teach that in the absence of the δ subunit other T cell receptor subunits are synthesized at their normal rates, but are retained in the endoplasmic reticulum where they are degraded at different rates, and that the stability of individually expressed T cell receptor subunits could be increased by coexpression of a different T cell receptor subunit (The Journal of Cell Biology, Vol. 109, July 1989, pages 73-83, see page 74 column 1 last paragraph; page 81 column 2 through page 82 column 1). Bonifacino et al. also teach that failure of T cells to synthesize sufficient ζ subunit results in the delivery of incomplete T cell receptor complexes to lysosomes for degradation, whereas failure of T cells to synthesize sufficient α or β subunit results in the retention of incomplete T cell receptor complexes in the endoplasmic reticulum

where they are degraded (page 74 column 1 first paragraph; page 75 column 2 first paragraph; page 80 column 2 third paragraph).

Additionally, proper assembly may require the presence of cellular factors other than the different polypeptides. For example, Yu et al. teach that heme incorporation plays an important role in cytochrome b_{558} assembly, and that that cytochrome b_{558} subunit stability may be dependent on heme incorporation as well as heterodimer formation (The Journal of Biochemistry, 1997, Vol. 272, No. 43, pages 27288-27294, see page 272289 column 1 second and third paragraphs; page 27293 column 1 second paragraph through column 2 first paragraph).

The specification does not provide sufficient guidance for one skilled in the art to determine which different polypeptides to express, and where and at what level and under what conditions to express them in order to obtain a plant cell containing a properly assembled and functional non-plant multimeric protein, because the specification provides detailed guidance for making plant cells containing only one specific class of non-plant multimeric proteins, namely immunoglobulins.

Furthermore, while one of skill in the art could readily make transgenic plants plant cells containing nucleotide sequences known to encode the different polypeptides present in any non-plant multimeric protein, it would require undue experimentation for one skilled in the art to determine how to express those polypeptides in a manner that would allow for expression of all types of non-plant multimeric proteins such that they would be present at a level of at least 56 ng/mg of total protein in a plant extract, because the level of expression of any polypeptide or multimeric protein in any cell is unpredictable, as numerous variables may affect the level of expression. Variables which may affect the level of expression include but are not limited to the

type of promoter and terminator used in the expression vector, the plant species transformed by the expression vector, the type of tissue in which the polypeptide is expressed, the stability of the mRNA transcribed from the coding sequence, the translation efficiency of the mRNA, the stability of the individual polypeptides, and the extent of assembly of individual polypeptides into protein multimers. Accordingly, different levels of expression would be expected for different types of polypeptides and multimeric proteins, or for the same polypeptide expressed from different types of expression vectors, or for the same polypeptides and multimeric protein expressed in different species or in different tissues. For example, Applicant's own disclosure indicates that kappa chain accumulation was 40-fold greater, and gamma chain accumulation was 47-fold greater, when a signal sequence was present in the cDNA construct used to express kappa and gamma chain immunoglobulin subunits in plant cells (page 68 lines 15-33). The specification does not provide sufficient guidance for one skilled in the art to express at the claimed levels, without undue experimentation, all types of non-plant multimeric proteins, as the specification teaches a method of expressing only one type of non-plant multimeric protein at the claimed level.

Claim 21, and claims dependent thereon, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite in the recitation of "biologically functional". It is unclear in what way the multimeric protein is "biologically functional", as the specific identity of the multimer is unclear, and any protein would be presumed to have a "biologic" function.

Claim 21 is indefinite in the recitation of "at least two different polypeptides". The number of different polypeptides that the multimer may comprise is unclear, as the specific identity of the multimer is unclear, and the claim places no upper limit on the number of different polypeptides present in the multimer contained within the claimed plant cells. It is presumed that there is a limit to the number of different polypeptides that any particular multimer may comprise. The claim does not explicitly indicate the number of different polypeptides that the multimer may comprise by limiting the number of different polypeptides, and the claim does not implicitly indicate the number of different polypeptides that the multimer may comprise by indicating the nature of the multimer.

Claim 21 is indefinite in the recitation of "not normally produced by plants". It is unclear what type of polypeptides would be "not normally produced by plants". Would such polypeptides be produced by plants as a consequence of the expression of native genes under abnormal or atypical conditions? Would such polypeptides be produced by plants as a consequence of the expression of foreign genes as a consequence of natural gene transfer such as infection by a pathogen? Would such polypeptides be produced by plants as a consequence of the expression of foreign genes as a consequence of artificial gene transfer such as by microparticle bombardment or *Agrobacterium* mediated transformation?

Claim 26, and claims dependent thereon, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite, as it is unclear how a multimeric protein "forms" a binding site. Does Applicant mean that the multimeric protein "contains" a binding site?

Claim 63, and claims dependent thereon, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "derived", as it is unclear what would be retained by the algal plant from which the plant cell is "derived", and it is unclear what aspects of the algal plant would be possessed by a cell "derived" from it. It is suggested that the claim be amended to recite "obtained" rather than "derived".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21, 24-40, 43, 50, 54-63, 69-80 and 101-102 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-69 of U.S. Patent No. 6,417,429. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 21, 24-40, 43, 50, 54-63, 69-80 and 101-102 are drawn to transgenic plants comprising plant cells containing nucleotide sequences encoding a biologically functional multimeric protein comprising at least two different polypeptides not normally produced by plants, including immunoglobulin multimers, and the biologically functional multimeric protein encoded by said sequences, whereas claims 1-69 of U.S. Patent

No. 6,417,429 are drawn to transgenic plants comprising plant cells containing nucleotide sequences encoding immunoglobulin multimers that comprise at least two different polypeptides not normally produced by plants, and the immunoglobulin multimers encoded by said sequences.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (703) 605-1210. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CC
September 11, 2003

PHUONG T. BUI
PRIMARY EXAMINER 9/11/03